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Docket No.: 6670/0J501

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Moussa HOUMMADY

Serial No.: 09/882,308 Art Unit: N/A

Filed: June 15, 2001 Examiner: N/A

For: SYSTEME DE DISTRIBUTION PARALLELE ET SELECTIVE

CLAIM FOR PRIORITY

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Applicant hereby claims priority under 35 U.S.C. Section 119 based on Canada application No. 2,311,622 filed June 15, 2000.

A certified copy of the priority document is submitted herewith.

Respectfully submitted,

Dated: July 9, 2001

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This is to certify that the documents attached hereto and identified below are true copies of the documents on file in the Patent Office.

Specification and Drawings, as originally filed, with Application for Patent Serial No: **2,311,622**, on June 15, 2000, by **MOUSSA HOUMMADY**, for "Sub-Nanoliter Liquid Drop Dispensing System and Method Therefor".

Agent certificateur/Certifying Officer

June 20, 2001

Date

Canada

(CIPO 68)
01-12-00

OPIC CIPO

TITLE OF THE INVENTION

SUB-NANOLITER LIQUID DROP DISPENSING SYSTEM AND METHOD THEREFOR

FIELD OF THE INVENTION

The present invention relates to liquid drop dispensing systems. More specifically, the present invention is concerned with a sub-nanoliter liquid drop dispensing system.

BACKGROUND OF THE INVENTION

Recent progress in the genomic field led to increasing speed of expirementation, minimized sample volumes and parallel operation systems. This brought different techniques for biochemical liquid handling, such as micro-spotting systems, micro pipetting with piezoelectric actuators, and more recently, inkjet technology. The driven force for these technologies is micro-array preparation and DNA-Chips preparation by printing, in major cases, pre-synthesized oligonucleotides on a glass or a quartz surface.

Some techniques of the prior-art, such as micro pipetting with piezoelectric actuators and inkjet-based methods, are particularly interesting since they allow dropping of pre-synthesized oligonucleotides or in-situ synthesis.

However, a drawback of such techniques is that the geometry of these liquid dropping systems does not allow both high-speed and high-density screening.

According to high-density criteria combined with short time micro-array preparation, there is a need for Ultra-High ThroughPut (UHTP) systems, which allow the printing of very small amount of biological samples, in batches, with a spatial resolution comparable to a photo-lithographical method for DNA fixation.

OBJECTS OF THE INVENTION

An object of the present invention is therefore to provide an improved sub-nanoliter liquid drop dispensing system.

BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1 is a sectional view of a sub-nanoliter liquid drop dispensing system according to a first embodiment of the present invention;

Figure 2 is an isometric view of a plurality of dishes of th liquid drop disp nsing syst m of Figure 1;

Figure 3 is an isometric view of a one of the dish of Figure 2;

Figure 4 is a sectional view of a sub-nanoliter liquid drop dispensing system according to a second embodiment of the present invention;

Figure 5 is a sectional view of a sub-nanoliter liquid drop dispensing system according to a third embodiment of the present invention;

Figure 6 is an isometric view of a matrix of pyramidal nozzles according to a first embodiment of the present invention;

Figure 7 is an isometric view of a matrix of cylindrical nozzles according to a second embodiment of the present invention.

Figure 8 is a photographic image of a pyramidal nozzle according to the first embodiment of the present invention; and

Figure 9 is a photographic image of a pyramidal nozzle according to a second embodiment of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Generally stated, the present invention concerns an ultra high throughput, a batch sub-nanoliter liquid drop dispensing system with integrated reservoirs, micro-channels, and individual drop ejection actuators.

Turning now to Figures 1 to 4 of the appended drawings, a sub-nanoliter liquid drop dispensing system 10, according to a first embodiment of the present invention, will be described.

The liquid drop dispensing system 10 comprises a plurality of dishes 12 embedded in a substrate 14 (Figure 2), deformable membranes 16 covering the dish and an actuator in the form of a thin film 17 having magnetic properties.

Turning now to Figure 3, the dish 12 will be described in more detail.

The dish 12 includes a tapered liquid sample reservoir 18 provided with a nozzle 19 (Figure 1) and having an aperture 20 at its narrow end, a pumping chamber 22 adjacent to the reservoir 18, and a microchannel 24 for handling liquid samples to the reservoir 18.

Although th res rvoir 18 is illustrated as being pyramidal in shap , it may have other configurations, such as cylindrically

integrated and cubic without departing from the spirit and nature of the present invention.

The reservoir 18 may advantageously be formed in an etchable material, using, for example, a method that allows the fabrication of microwells with different shapes.

The sizes of the reservoir 18, of the nozzle 19, and of the aperture 20 are chosen according to the application and the desired density.

More specifically, the nozzle 19 is configured and sized to allow control of the droplet sizes. Indeed, droplet size control has been found advantageous, for example, in the field of micro or nano-array printing which allows the density of printable material such DNA Chips to increase. In addition, it has been found advantageous to include a nozzle 19 having a high aspect ratio.

In order to build a matrix of nozzles 19 with high aspect ratio (side walls 26), different methods can be used, such as photolithography bulk and surface micro-machining.

Methods such as wet chemical etching, deep reactive ion etching, electro-forming of materials, electro-discharge micro-machining, molding, hot embossing and polymerization may be used to form th reservoir 18, nozzl 19 and ap rture 20.

Figure 6 illustrates a matrix of pyramidal nozzles 40, with individual liquid sample reservoirs according to a first embodiment of the present invention. Each of the pyramidal nozzles includes side walls 42 and an aperture 44.

Figure 7 illustrates a matrix of cylindrical nozzles 48 with individual sample reservoirs 46. Each nozzle 48 includes an aperture 50.

Figure 8 is a photo illustrating a pyramidal nozzle according to the first embodiment of the present invention. The pyramidal nozzle is provided with an aperture 52 of 15x15 μm^2 and is covered with a protective layer of silicon dioxide.

Figure 9 is a photo illustrating a pyramidal nozzle, similar to the nozzle of Figure 8, with an aperture of 5x5 μm^2.

Methods such as electroforming, electroplating and molding allow the fabrication of the nozzle 19 in a different material from that of reservoir 18.

The microchannel 24 can be made of materials such as, for example, glass, quartz, silicon, electroforming materials and PDMS. The width and depth of the microchannel 24 is typically micrometric and advantageously allows the flow of liquid from input holes (not shown in the figures) to the pumping chamber 22. To prevent sticking of biological samples in the microchannel 24, its inner surfaces are advantageously treated to have specific hydrophobic or hydrophilic properties.

Examples of materials that can be used for the reservoirs 18 or for the microchannels 24 with the pumping chambers 22 include, but are not restricted to, silicium, SiO_2, Glass, quartz, polymers, resins, plastics and metals (electroformed or processed).

As can be better seen in Figure 1, a membrane 16 is advantageously provided to cover the dishes 12. The deformation of the membrane 16 can trigger either one or both of the following functions: pumping liquid sample from microchannels and individual drop injection.

The deformation of the membrane 16 is triggered by a thin film 17 having magnetic properties. An electrical coil 28 is advantageously used to selectively generate a magnetic field that allows deformation of the membrane 16 without direct contact. The membrane 16 can advantageously be deformed in both directions.

Other actuators can alternatively be used to cause deformation of the membrane 16, including actuators based on electro-magnetic forces (piezoelectric), thermal expansion, electro-mechanical stress, and electrostatic forces. Any other actuators allowing static or dynamic deformation of the membrane 16 can also be used without departing from the spirit of the present invention.

Figure 4 illustrates the use of a piezoelectric thin film 30, between lower and upper conductive electrodes 32 and 34. The membran 16 may b d formed by applying a t nsion b tween the

electrodes 32 and 34. Such actuator allows deformation of the membrane 16 in static or in resonance.

When thermal expansion is used, a thin film, having a thermal expansion coefficient sufficiently different from the one of the membrane 16, is deposited on the membrane 16. Heating of the film will then induce a deformation of the membrane 16.

Alternatively, the membrane 16 and the actuator 17 may be replaced by other means to cause injection of droplets. Such means include an electrical field applied between the reservoir and the liquid sample input reactors to cause electrophoretic mobility, low pressure liquid attraction from the aperture 20 of the nozzle 19, electrospray (allowing extraction of droplets by inducing an electro-magnetic force), and deformation of the aperture 20 or combination thereof. Since these techniques are believed to be well known in the art, they will not be discussed in more detail.

To independently trigger the pumping and the liquid drop injection, independent actuators may be used, as illustrated in Figure16, where an actuator for drop injection 36, and an actuator for liquid sample pumping 38 are shown.

It is to be noted that each reservoir 18 may contain different liquid samples. Moreover, the liquid drop dispensing system 10 may advantageously be provided with specific arrangements of connected res rvoirs through microchannels (lines, columns or specific blocs).

A liquid drop dispensing system of the present invention allows for example:

- Injection of droplets in high density with volume of 1 micro liter and 1 hundredth of a picoliter;
- Individual addressing on demand on an important surface;
- Integration of all elements of the liquid drop dispensing system that can be processed in whole or in part;
- Obtaining of hollow injectors that can have an high aspect ratio;
- Obtaining of injectors having miniature and precise apertures for controlling the size of the liquid droplets;
- Obtaining of injectors provided with apertures of different sizes;
- Usage of reservoirs that can include different reagents; and
- Usage of individual or custom-built injectors.

It is to be noted that the operation of the liquid drop dispensing system may be reversed to pump and then carry small quantities of liquid (for example PCR product) from one place to another. Indeed, in this cas , th liquid is pumped through th apertures 20 to fill th reservoirs 18 from microarray, or by performing a parall l processing

such as PCR. The delivery of the liquid is later performed by injection.

A liquid drop dispensing system, according to an embodiment of the present invention, may be used in many applications, including, for example:

- High speed screening that allows distribution and controlled manipulation of a small quantity of liquid, such as biological substances (including DNA, RNA, proteins, blood, etc.), reagents, drugs and chemical products;
- High rate oligonucleotide synthesis to prepare, for example, biomolecular computing devices;
- Preparation of biomolecular computing devices (DNA, RNA, proteins, etc.);
- Controlled delivery of medication;
- Controlled delivery of biological and/or chemical substances in cells or tissues (mechanical injection that can be performed with or without other techniques such as electroporation); and
- High rate genomic, proteomic, transgenic and in-vitro services.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified without departing from the spirit and nature of the subject invention, as defined in th appended claims.

WHAT IS CLAIMED IS:

1. A sub-nanoliter liquid drop dispensing system as described in the present application.

2. A method for dispensing liquid drops as described in the present application.

3. The use of the system described in claim 1 for dispensing drops of oligonucleotides.

ABSTRACT OF THE DISCLOSURE

A sub-nanoliter liquid drop dispensing system is described herein. The liquid drop dispensing system comprises a plurality of dishes embedded in a substrate, and a deformable membrane covering the dish. The dish includes a tapered liquid sample reservoir provided with a nozzle having an aperture at its narrow end, a pumping section adjacent to the reservoir and a microchannel for handling to the reservoir liquid samples.

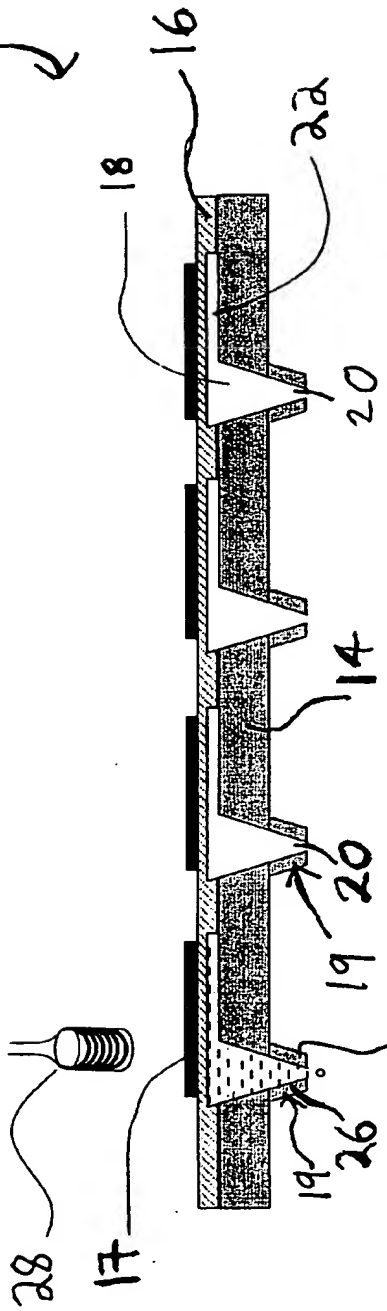

FIG. 1

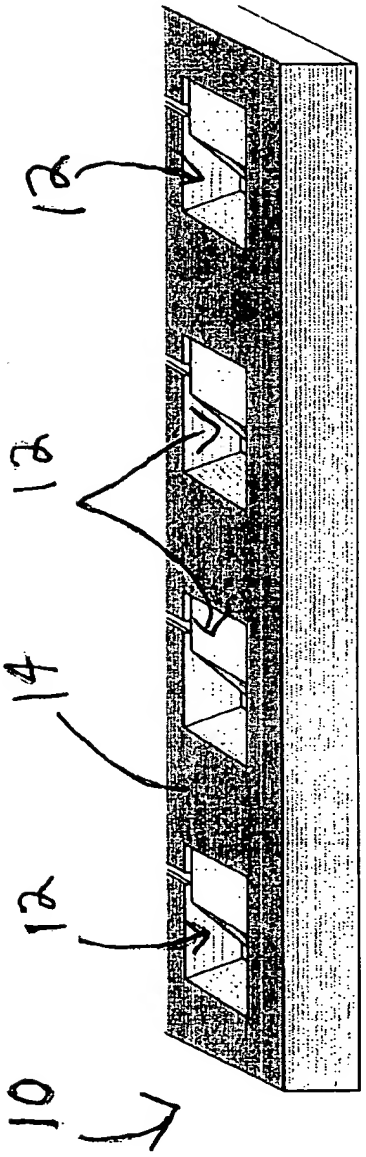

FIG. 2

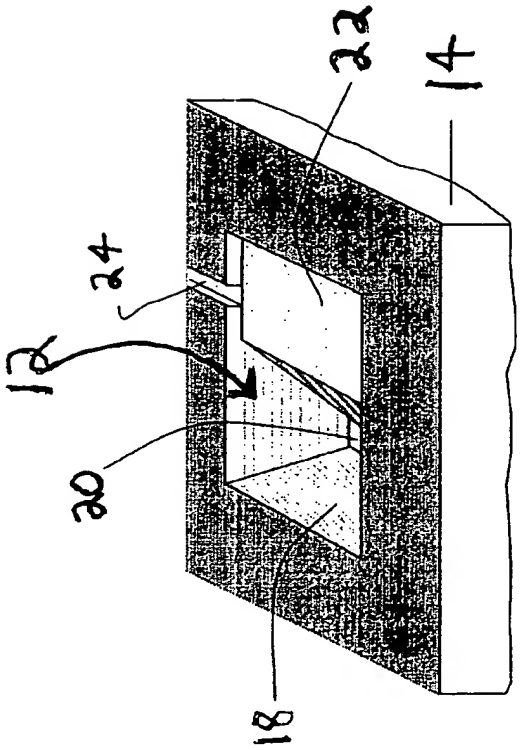

FIG. 3

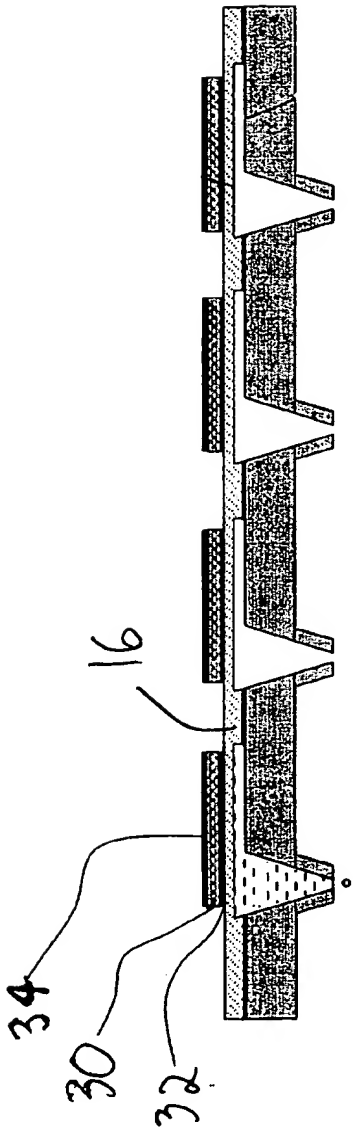

FIG. 4

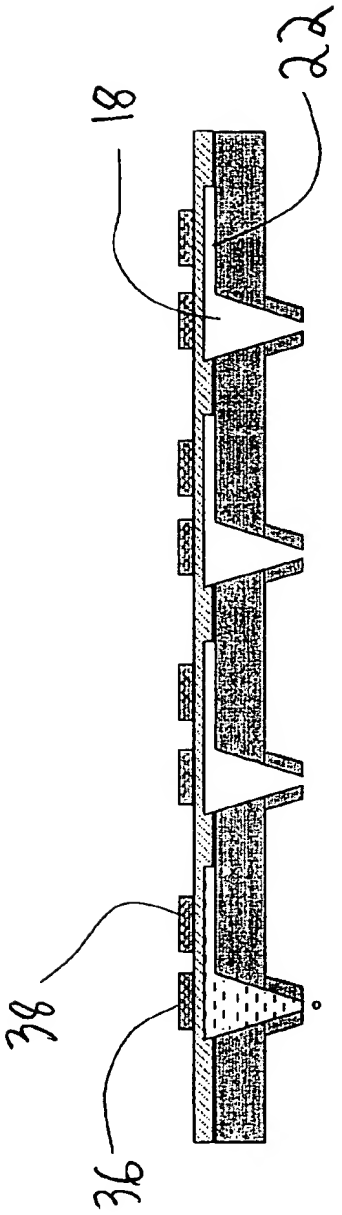

FIG. 5

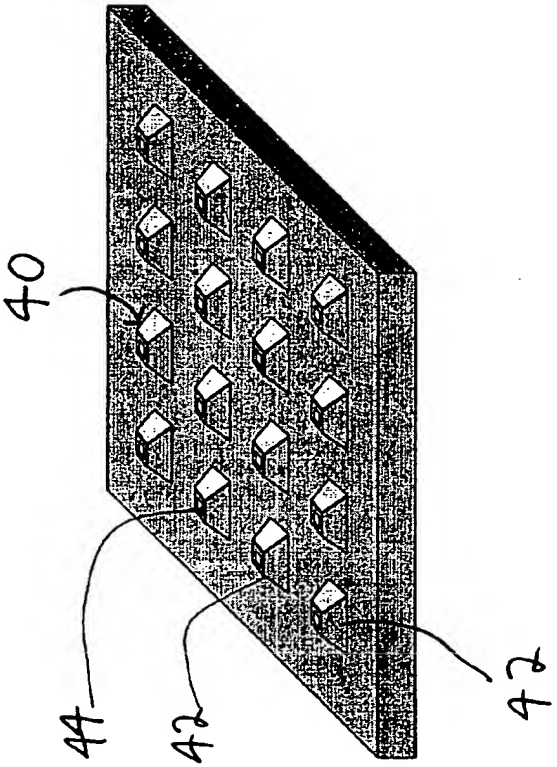

FIG. 6

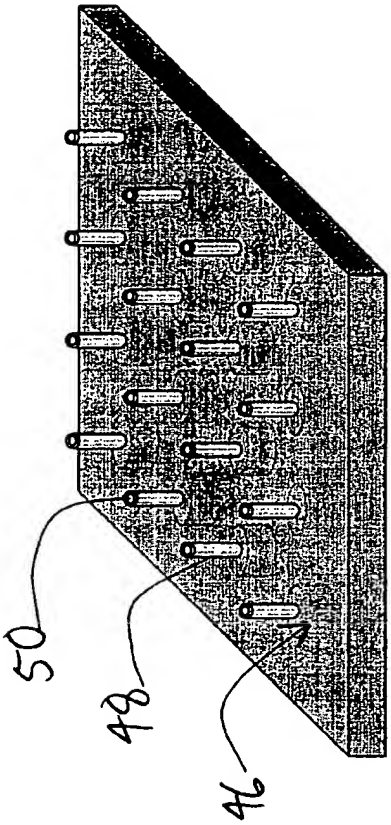

FIG. 7

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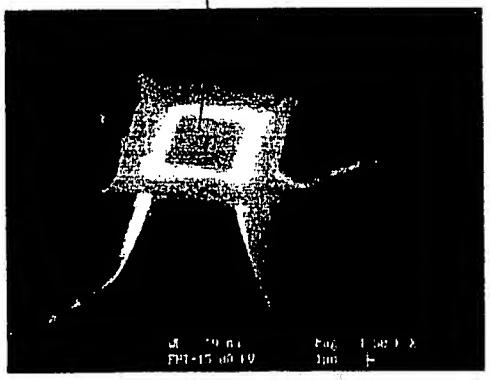

FIG. 8

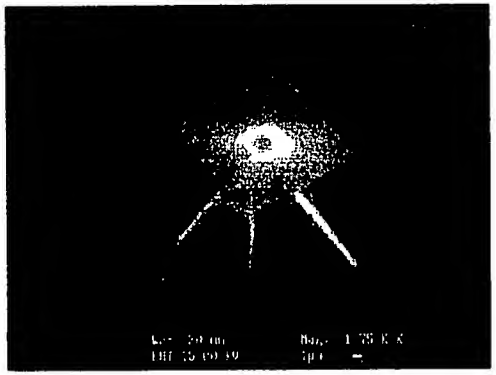

FIG. 9